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EXAMINER	
STAPLES, MARK	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/575,804	HAN, JAIN	
	Examiner	Art Unit	
	MARK STAPLES	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37,69 and 79* is/are pending in the application.

4a) Of the above claim(s) *11,13,26, 36, 69 and 79* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,12,14-25,27-35 and 37* is/are rejected.

7)☒ Claim(s) *1* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 April 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/21/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I claims 1-37 in the reply filed on 04/03/2009 is acknowledged. The traversal is on the ground(s) that there is a special technical feature linking the claims. This is not found persuasive because there is no special technical feature linking the claims as the methods of claims 1 and 37 are found in the prior art (as given in the rejections under 35 U.S.C. 102 below).

The requirement is still deemed proper and is therefore made FINAL.

Claim 69 and 79 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 04/03/2009.

2. Claims 11, 13, and 36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 04/03/2009.

3. Applicant's election with traverse of the species of claim 24 in the part to bacteria and claim 26 in the reply filed on 04/03/2009 is acknowledged. The traversal is on the ground(s) that the species are dependent are specific forms of the invention claimed in

independent claims. This is not found persuasive because the species is claimed in the separate and distinct dependent claim 26 and there would an undue search burden to examine all of the species. Should any generic claim be found allowable, claims of the species withdrawn but dependent from an allowable generic claim will be considered for rejoinder.

The requirement is still deemed proper and is therefore made FINAL.

Claim 24 in the part to bacteria and claim 26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 04/03/2009.

In summary, claims 1-10, 12, 14-23, 24 in part the part to virus, 25, 27-35, and 37 as filed on 04/03/2009 will be fully examined for patentability.

Specification

4. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The title should reflect that the methods use primers with binding tags.

5. The disclosure is objected to because of the following informalities: the Table on pages 42 and 43 are illegible in parts and the Table is indicated as being both Table 8 and Table 4. Page numbers are also missing for pages 42 and 43. Appropriate correction is required.

6. The use of the trademark LUMINEX® has been noted in this application. It and any other trademarks should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Applicant is advised to scan the entire application to ensure trademark usage in all the places where it appears in the application is in compliance with the current office guidelines.

Sequence Rules Compliance

7. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132.

Applicant is given time of reply to this office action within which to comply with the sequence rules, 37 C.F.R. §§ 1.821-1.825. Failure to comply with these requirements will result in **abandonment** of the application under 37 C.F.R. § 1.821(g).

Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the period for response beyond the six month statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

Pages 35-39 respectively contain sequences without SEQ ID NOs. If these sequences are included in the sequence listing provide by Applicant, the specification should be amended to include the SEQ ID NOs. If these sequences were not included in the sequence listing filed 04/13/2006, Applicant should provide a substitute sequence listing and a CRF that include those sequences.

Claim Objections

8. Claim 1 is objected to because of the following informalities: there is an stray underline mark in step b in the phrase "amplified_using". Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 22 and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. Claim 22 recites the limitation "enhancement primers" in line 2. There is insufficient antecedent basis for this limitation in the claim. It is further noted that the specification does not define “enhancement primers”; the term "enhancement primers" is not found in the specification.

12. Claim 25 recites the term "including." This term has the same effect as using the phrase "such as." Regarding claim 8, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d). The scope of the claim is unclear, since it is not apparent if the scope is limited by what follows the term, or if the terms following the term "including" are actually a part of the claimed invention.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

14. Claims 1-10, 12, 14-22, 27, 29-34, and 37 are rejected under 35 U.S.C. 102(e) as being anticipated by Chen (Chen ‘970, United States Patent 7,262,030 issued 2007 with priority to Application NO. 10/476,970 with priority to PCT PCT/US02/14431 in English and filed 08/30/2002).

Regarding claims 1-3, 20, 27, and 37, Chen teaches methods for multiplex primer-based amplification with inner and outer primers of a selective target sequence from a plurality of agents of genotypes (entire patent especially the Abstract), said target sequence being different for each agent, said method comprising:

a. carrying out a first amplification reaction for each target sequence to be amplified which is a first round of PCR (see claims 1 and 11) using

i) as a template, a nucleic acid from each of said plurality of agents, said nucleic acid containing said target sequence (see claims 1 and 11, and column 7 lines 8-67);

ii) a first pair of target enrichment primers hybridizing to said nucleic acid and bracketing said target sequence which are outer primers (see claim 1, Figures 1 and 2 and which can be P1 primer and one of either P3 or P4 primers, and column 7 lines 8-67);

iii) a second pair of target enrichment primers hybridizing to said nucleic acid and bracketing said target sequence, said second pair of target enrichment primers being located proximate to said target sequence and one of the second pair of target enrichment primers comprising at its 5' end a binding tag corresponding to the sequence of one of a pair of target amplification primers and the other of the second pair of target enrichment primers comprising at its 5' end a binding tag corresponding to the sequence of the other of said pair of target amplification primers (see claims 1 and 11, and Figures 1 and 2 and which can be P1 and P3 primers); and

iv) amplification reagents and conditions for said first amplification reaction such that the first amplification reaction generates a plurality of first amplification products, wherein at least a portion of the first amplification products contain said target sequence and at

least one complement of the binding tag for one of said target enrichment primers thereby forming at least one binding site for at least one of said target amplification primers (which includes PCR amplification, see claims 1 and 11, and Figures 1 and 2); and

b. carrying out a second amplification reaction for each target sequence to be amplified which is a second round of PCR (see claims 11, 13, and 15) using

i) as a template, said portion of the first amplification products containing said at least one binding site for at least one of said target amplification primers (see claims 11, 13, and 15);

ii) at least one of said first pair of target amplification primers binding to its corresponding binding sites on said portion of said first amplification products (see claims 11, 13, and 15); and

iii) amplification reagents and conditions for said second amplification reaction which is PCR such that the second amplification reaction generates a plurality of second amplification products containing the target sequence (see claims 11, 13, and 15).

Regarding claims 4-7 and 21, Chen teaches primers varying in length and primers which are 23 nucleotides in length (see sequences 5-9 in column 23 line 79 to column 26 line 40)

Regarding claims 8 and 9,Chen teach where the target enrichment primers are at a low concentration relative to the high concentration of the target amplification primers (see claim 15). Further regarding claim 9, Chen teaches the low concentration of 10 nM

which is 0.01 uM and greater than 0.002 uM and teaches the high concentration of 100 nm which is 0.1 uM and approximately 0.2 uM.

Regarding claim 10, Chen teaches the target primary primers are limited for example to about 1-5% for a regular PCR see which thus is not sufficient for exponential amplification; and that the secondary primers amplify unlimited which is sufficient for exponential amplification (see column 9 lines 4-22).

Regarding claim 12, Chen teaches the inner primers which are target enrichment primers can vary in concentration with one inner primer being 600 nm and the others 400 nm (see column 7 lines 43-45).

Regarding claim 14, Chen teaches that the target amplification primers can vary in concentration, that is that one primer may have a higher concentration, in accordance with the length of the primers (see column 14 lines 9-28).

Regarding claims 15 and claims 29-34, Chen directly detecting fluorescently labeled oligonucleotides ligated to a target (see column 11 lines 61-64) and where the ligation of the target is directly combined with the second amplification PCR reaction, resulting in a closed tube assay (see column 13 lines 42-45).

Regarding claims 16-19, Chen teaches various cycles, times, and temperatures for amplification processes (entire patent) and teaches that these can be varied and that their methods with primers to two domains facilitates primer annealing to avoid problems with thermocycling (see column 8 lines 1-23) and with one example being:

> "The cycling condition was 95°C. for 10 min, followed by 10 cycles of 95°C. for 45 sec., 65°C. for 5 sec., ramping to 55°C at 0.1° C./sec and 55°C. for 90 sec. . . . . The cycling conditions for the second reaction was following: 95°C. for 10 min,

> followed by 30 cycles of 95°C. for 45 sec., 55°C. for 90 sec." (see column 6 lines 35-47).

Further regarding claims 16-19, Chen teaches as noted above. Chen teaches methods of amplifying nucleic acids with various conditions of cycles, times, and temperatures.

Chen does not specifically teach the exact conditions of instant claim 16-19.

It would also have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the amplification conditions as used by Chen since these differences in the amplification conditions would not be expected to greatly alter the amount of amplification products generated. Though the effective concentration of a product at any given condition might be lower, this would be offset by the longer cycle times and or more cycles. "For example, one could use 70°C. as the annealing temperature for the primary reaction and cycle 10 times, then the temperature could be lowered to 50°C. for 30 more cycles" (see last sentence of paragraph 0059). This is consistent with the Federal Circuit decision in In re Peterson, 65 USPQ2d 1379, 1382 (Fed. Cir. 2003) "We have also held that a prima facie case of obviousness exists when the claimed range and the prior art range do not overlap but are close enough such that one skilled in the art would have expected them to have the same properties." Thus, an ordinary practitioner would have recognized that the conditions for amplification could be adjusted to maximize the desired results. As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of amplification conditions was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art. As noted, a skilled artisan would expect the claimed conditions for amplification to have nearly identical results for the amount of amplification products. Thus, an ordinary practitioner would have recognized that the results could be adjusted to maximize the desired results.

Regarding claims 22 and 23, Chen teaches at least three amplification primer pairs of: (1) inner primer pair P1 and P2, (2) outer primer pair P1 and P3, and (3) inner primer pair P4 and P2 (see Figure 1, see column 7 lines 8-32 for the first two primer pairs, and see column 7 lines 33-66 for the third primer pair and noting that even further primer pairs are described and P4 might be designed to be in another primer pair). The "enhancement primers" of claim 22 are interpreted to be primers used in the method of instant claim 1.

15. Claims 37 is rejected under 35 U.S.C. 102(e) as being anticipated by Chen (Chen '381, United States Patent Application 20030096277, published 05/22/2003, Application NO. 10/231381 filed 08/30/2002 with priority to 60/315776 filed 08/30/2001).

Regarding claim 37, Chen teaches methods for multiplex primer-based amplification of a target sequence from a plurality of agents of genotyping (entire patent

especially the Abstract), said target sequence being different for each agent, said method comprising:

a. carrying out a first amplification reaction for each target sequence to be amplified which is a first round of PCR (see claim 10)

using

i) as a template, a nucleic acid from each of said plurality of agents, said nucleic acid containing said target sequence (see claim 10);

ii) a first pair of target enrichment primers hybridizing to said nucleic acid and bracketing said target sequence, each of the first pair of target enrichment primers comprising at its 5' end a binding tag corresponding to the sequence of one of a pair of target amplification primers and the other of the second pair of target enrichment primers comprising at its 5' end a binding tag corresponding to the sequence of the other of said pair of target amplification primers (see claim 10, Figures 1 and Figure 2A especially elements 10A, 10B, and 30, and paragraph 0019); and

iii) amplification reagents and conditions for said first amplification reaction such that the first amplification reaction generates a plurality of first amplification products, wherein at least a portion of the first amplification products contain said target sequence and at least one complement of the binding tag for one of said target enrichment primers thereby forming at least one binding site for at least one of said target amplification primers (see claim 10, Figures 1 and Figure 2A especially elements 10A, 10B, and 30, and paragraph 0019); and

b. carrying out a second amplification reaction for each target sequence to be amplified which is a second round of PCR (see claim 10) using

i) as a template, said portion of the first amplification products containing said at least one binding site for at least one of said target amplification primers (see claim 10, Figures 1 and Figure 2A especially elements 20A, 20B and 40, paragraph 0019, and noting that this second primer of Chen is the target amplification primer of the instant claim);

ii) at least one of said first pair of target amplification primers binding to its corresponding binding sites on said portion of said first amplification products (see claim 10, Figures 1 and Figure 2A especially elements 20A, 20B and 40, paragraph 0019, and noting that this second primer of Chen is the target amplification primer of the instant claim); and

iii) amplification reagents and conditions for said second amplification reaction such that the second amplification reaction generates a plurality second amplification products containing the target sequence (see claim 10 for PCR).

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 1-10, 12, 14-23, and 27-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen (Chen '381, United States Patent Application 20030096277, Application No. 10/231381, published 05/22/2003, filed 08/30/2002), Jeffreys (United States Patent 5,811,235 Issued 1998), and as further evidenced by Erlich et al. (United States Patent 5,314,809 issued 1994) and by QIAGEN (2002).

Regarding claims 1 and 28, Chen teaches methods for multiplex primer-based amplification of a target sequence from a plurality of agents of genotypes (entire publication especially the Abstract), said target sequence being different for each agent, said method comprising:

a. carrying out a first amplification reaction for each target sequence to be amplified which is a first round of PCR (see claim 10) using

i) as a template, a nucleic acid from each of said plurality of agents, said nucleic acid containing said target sequence;

ii) a first pair of target enrichment primers hybridizing to said nucleic acid and bracketing said target sequence (see claim 10, Figures 1 and Figure 2A especially elements 10A, 10B, and 30, and paragraph 0072 noting first primers SC 22, SC 23, SC 24 for marker SC 22 and second primers SC 22, SC, 31, SC 32, SC 33 fro marker SC 31; and see paragraph 0019);

iii) a second pair of target enrichment primers hybridizing to said nucleic acid and bracketing said target sequence, said second pair of target enrichment primers being located proximate to said target sequence and one of the second pair of target enrichment primers comprising at its 5' end a binding tag corresponding to the

sequence of one of a pair of target amplification primers and the other of the second pair of target enrichment primers comprising at its 5' end a binding tag corresponding to the sequence of the other of said pair of target amplification primers; and

iv) amplification reagents and conditions for said first amplification reaction such that the first amplification reaction generates a plurality of first amplification products, wherein at least a portion of the first amplification products contain said target sequence and at least one complement of the binding tag for one of said target enrichment primers thereby forming at least one binding site for at least one of said target amplification primers (see claim 10, Figures 1 and Figure 2A especially elements 10A, 10B, and 30, and paragraph 0072 noting first primers SC 22, SC 23, SC 24 for marker SC 22 and second primers SC 22, SC, 31, SC 32, SC 33 fro marker SC 31; and see paragraph 0019); and

b. carrying out a second amplification reaction for each target sequence to be amplified which is a second round of PCR (see claim 10) using

i) as a template, said portion of the first amplification products containing said at least one binding site for at least one of said target amplification primers (see claim 10;

ii) at least one of said first pair of target amplification primers binding to its corresponding binding sites on said portion of said first amplification products by teaching; “at least one secondary primer having a second homologous portion which comprises sequences identical to those of said non-homologous portion of said primary primer” (see claim 10, Figures 1 and Figure 2A especially elements 20A, 20B and 40,

paragraphs 0072 and 0019, and noting that this second primer of Chen is the target amplification primer of the instant claim); and

iii) amplification reagents and conditions for said second amplification reaction which is PCR such that the second amplification reaction generates a plurality of second amplification products containing the target sequence (see claim 10).

Further regarding claim 28, it is noted that Chen teaches the target amplification primers necessarily have a means for detection which is their sequences are used as the means to detect the target.

Regarding claim 1, Chen suggests but does not specifically teach that the first amplification reaction comprises two primer pairs to the same target sequence.

Regarding claims 4-7 and 21, Chen teaches different length of the first pair target enrichment primers varying in length for 10-40 and 10-30 nucleotides (see Table 1). Further regarding claims 4-7 and 21, Qiagen teaches stanrad primers range from 18-30 nucleotides which overlaps with the claimed ranges (see Table 12 on p. 30).

Regarding claims 8-10, 12, 19, and 21, Chen teaches the target enrichment primers are a low concentration of about 0.1 to about 0.5 nM which is only about 1% to 2% for regular exponential PCR) and the target amplification primers which are the secondary primers of Chen are at a higher concentration of about 25 to about 50 nM which is non-limiting and thus necessarily is sufficient for exponential amplification (see claim 10 and paragraph 0061). The approximate ranges of Chen thus fall within the claimed ranges as about 0.5 nm which is about 0.0005 uM is about 0.002 uM; and about 50 nM is about 0.05 uM which is about 0.2 uM.

Regarding claim 14, Chen teaches one target amplification primer at 100 NM and a second reverse primer at the higher concentration of 300 nM (see paragraph 0105) and also teach target amplification primers of SC 4 at 25 nM, SC 5 at 26 nM, and SC 6 at the higher concentration of 50nM (see paragraph 0072) and also being labeled.

Regarding claim 15, Chen teaches at least one of the primers is the SC 4 primer which is detectably labeled with BODIPY Fluorescein and which is used at the higher concentration of 50 nM than the 25 nM concentration of the SC 5 primer (see last sentence of paragraph 0073 and Table 1).

Regarding claims 16 and 18, Chen teaches limited cycles of about 5 to about 10 cycles for target enrichment (see paragraph 0061 and see paragraph 0105 for 10 cycles) and teaches non-limiting PCR fro the second amplification and thus necessarily teaches the second amplification can have at least 10 cycles of PCR (see paragraph 0061 and which can be 30 cycles as given in paragraph 0105). It is noted that the second amplification process of Chen is also necessarily selective as the primers used are selective for the target to be amplified.

Regarding claims 17 and 19, Chen teaches various cycles, times, and temperatures for amplification processes and teaches that these can be varied (see last two sentences of paragraph 0059) and gives examples:

> "The thermal cycling conditions were 95°C for 10 min followed by 10 cycles of 95°C for 30 sec, 65°C for 5 sec, ramp at -0.1.degree. C./sec to 55°C, 55°C. for 1.5 min. . . . The secondary reaction used the conditions of 25 cycles of 95°C for 30 sec, 60°C. for 1.5 min with a final extension at 72°C for 10 min." (see paragraph 0071).

Further regarding claims 17 and 19, Chen teaches as noted above. Chen teaches methods of amplifying nucleic acids with various conditions of cycles, times, and temperatures.

Chen does not specifically teach the exact conditions of instant claim 17 and 19.

It would also have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the amplification conditions as used by Chen since these differences in the amplification conditions would not be expected to greatly alter the amount of amplification products generated. Though the effective concentration of a product at any given cycle might be lower, this would be offset by the longer cycle times and or more cycles. "For example, one could use 70°C. as the annealing temperature for the primary reaction and cycle 10 times, then the temperature could be lowered to 50°C for 30 more cycles" (see last sentence of paragraph 0059). This is consistent with the Federal Circuit decision in In re Peterson, 65 USPQ2d 1379, 1382 (Fed. Cir. 2003) "We have also held that a prima facie case of obviousness exists when the claimed range and the prior art range do not overlap but are close enough such that one skilled in the art would have expected them to have the same properties." Thus, an ordinary practitioner would have recognized that the conditions of amplification could be adjusted to maximize the desired results. As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of amplification conditions was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art. As noted, a skilled artisan would expect the claimed conditions for amplification to have nearly identical results for the amount of amplification products. Thus, an ordinary practitioner would have recognized that the results could be adjusted to maximize the desired results.

Regarding claim 20, Chen teaches the methods that select for SNPs (see paragraph 0079) with a bias towards the first amplification products so that they may be detected (entire publication).

Regarding claim 22, Chen teaches several pairs of primers (entire publication, especially Table 1). The "enhancement primers" of claim 22 are interpreted to be primers used in the method of instant claim 1.

Regarding claim 23, Chen teaches that multiple allele specific primers each paired with a reverse primer which is then multiple pairs of target amplification primers which are used in the methods (see Example 7 especially paragraph 0105).

Regarding claim 27, Chen teaches the design of primers for selecting the agent which is genotype of an allele (entire publication, especially the 2nd sentence of the Abstract).

Regarding claims 28-31, Chen teaches the primer comprise a means of detection of the target sequence which are labels selected from a detectable label selected from

the group consisting of fluorescent dyes, antibodies, enzymes, magnetic moieties, electronic markers, mass tags (see claims 1 and 5, paragraphs 0064 to 0067, and paragraph 0075) and FRET labels for direct detection (see paragraph 0066).

Regarding claim 32-34, Chen teaches detection oligonucleotides which are primers incubated with second amplification products to produce and detect a signal of agents which are alleles (see claims 1 and 5 and Abstract) and teaches a unique tag/label for a a given allele (see paragraph 0032). Chen further teaches the primer comprise a means of detection of the target sequence which are labels selected from a detectable label selected from the group consisting of fluorescent dyes, antibodies, enzymes, magnetic moieties, electronic markers, mass tags (see claims 1 and 5, paragraphs 0064 to 0067, and paragraph 0075) and FRET labels for direct detection (see paragraph 0066).

Regarding claims 1-3 and 28, Jeffreys et al. teach methods for multiplex primer-based amplification of a target sequence from a plurality of agents, said target sequence being different for each agent (entire patent, especially claims 1-11), said method comprising:

a. carrying out a first amplification reaction in a two stage amplification (see column 12 lines 1-25) for each target sequence to be amplified using

i) as a template, a nucleic acid from each of said plurality of agents, said nucleic acid containing said target sequence (see Figure 27 and Figures 15A, B, and C);

ii) a first pair of target enrichment primers hybridizing to said nucleic acid and bracketing said target sequence (see Figure 27, Figures 15A, B, and C, step 1 of Example 15 where there are four primers being a first pair and a second pair);

iii) a second pair of target enrichment primers hybridizing to said nucleic acid and bracketing said target sequence (see Figure 27 and Figures 15A, B, and C of Example 15 where there are four primers being a first pair and a second pair), said second pair of target enrichment primers being located proximate to said target sequence and one of the second pair of target enrichment primers comprising at its 5' end a binding tag which is TAG or tail corresponding/complementary to the sequence of one of a pair of target amplification primers the other of the second pair of target enrichment primers comprising at its 5' end a binding tag which is TAG or tail corresponding/complementary to the sequence of the other of said pair of target amplification primers (see Figure 27 and Figures 15A, B, and C and see step 1 of Example 15); and

iv) amplification reagents and conditions for said first amplification reaction such that the first amplification reaction generates a plurality of first amplification products which are amplfieid extension products , wherein at least a portion of the first amplification products contain said target sequence and at least one complement of the binding tag for one of said target enrichment primers thereby forming at least one binding site for at least one of said target amplification primers (see Figure 27 and Figures 15A, B, and C and see step 1 of Example 15); and

b. carrying out a second amplification reaction in a two stage amplification (see column 12 lines 1-25) for each target sequence to be amplified using

i) as a template, said portion of the first amplification products containing said at least one binding site for at least one of said target amplification primers (see Figure 27 and Figures 15A, B, and C and see step 2 of Example 15)

ii) at least one of said first pair of target amplification primers which is a tail specific pimer binding to its corresponding binding sites on said portion of said first amplification products (see column 12 lines 22-25, Figure 27 and Figures 15A, B, and C and see step 1 of Example 15); and

iii) amplification reagents and conditions for said second amplification reaction such that the second amplification reaction generates a plurality of second amplification products containing the target sequence (see column 12 lines 22-25, Figure 27 and Figures 15A, B, and C and see step 1 of Example 15).

It is noted that Jeffreys et al. teach a tail on a primer of the second primer pair but also teach the each primer of the second primer pair can have a tail and where each tail is different by teaching:

"In any relevant preceding aspect of the present invention different type specific primers may comprise different tail sequences to facilitate separation of the amplification products" (see column 7 lines 46-49).

Thus Jeffreys et al. suggest but do not specifically teach that each of the primers of the second primer of the amplification pair has a tail.

That tail primers were well known in the prior art is further evidenced by Erlich et al. but who do not specifically teach the two step amplification methods of claim 1.

Regarding claim 24, Erlich et al. teach detection of the AIDS virus.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods of Chen to have at least two primer pairs in the first amplification reaction by as suggested by Jeffreys with a reasonable expectation of success. The motivation to do so is provided by Jeffreys who teach in doing so that: "The invention also provides a novel method for the detection of diagnostic base sequences in one or more nucleic acids contained in a sample" (see last sentence of the Abstract). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

18. Claims 24 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over either one of (1) Chen '970 or (2) Chen '381, Jeffreys, Erlich et al., and Qiagen as applied to claim 1 above, and further in view of Elnifro et al. (2000)

Chen '970 teaches as note above but does not specifically teach detection of a virus.

Chen '381, Jeffreys, Erlich et al., and Qiagen teach as noted above but Chen '381, Erlich et al. do not specifically teach detection of a virus recited in claim 25.

Regarding claims 24 and 25, Elnifro et al. teach detection of Influenza A and Influenza B virises by multiplex amplification (entire article, especially Table 1).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the multiplex methods for detecting

nucleic acid seuqences of (1) Chen '970 or (2) Chen '381, Jeffreys, Erlich et al., and Qiagen by doing multiplex amplification to detect Influenza A and Influenza B viruses as suggested by Elnifro et al. with a reasonable expectation of success. The motivation to do so is provided by Elnifro et al. who teach: "More recently, it has been demonstrated that multiplex PCR is a useful and rapid diagnostic tool for the management of children with acute respiratory infections (36). This simplified hot start multiplex PCR allows simultaneous screening for nine different infectious agents (enterovirus, influenza viruses A and B, RSV, PIV types 1 and 3, adenovirus, Mycoplasma pneumoniae, and Chlamydia pneumoniae)" (see 1st sentence of the 2nd paragraph on p. 564). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

19. Claim 35 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chen '970 as applied to claims 1, 30, and 32 above, and further in view of Cheung (United States Patent 5,194,300 issued 1993).

Regarding claim 35, Chen teaches various labels for DNA detection but does not specifically teach fluorescent micropheres of claim 35.

Regarding claim 35, Cheung teaches fluorescent microspheres for detection of DNA (see Abstract). Thus it would have been obvious to one of ordinary skill in the art to use fluorescent microspheres for detection of DNA in the detection method of claim 35.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods of fluorescent detection of

Chen by using fluorescent microspheres as suggested by Cheung with a reasonable expectation of success. The motivation to do so is provided by Cheung who teach: "A single fluorescent microsphere is visible using standard fluorescent microscopy. Therefore the microspheres may be utilized not only to visualize cell surface anitgens but also DNA encoding for single genes, by means of a biotinylated DNA probe (see last two sentences of the Abstract). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

20. Claim 35 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chen '381, Jeffreys, Erlich et al., and Qiagen as applied to claims 1, 30, and 32 above, and further in view of Cheung (United States Patent 5,194,300 issued 1993).

Chen, Jeffreys, Erlich et al., and Qiagen teach as noted above.

Regarding claim 35, Chen teaches various labels for DNA detection but Chen, Jeffreys, Erlich et al., and Qiagen do not specifically teach fluorescent microspheres of claim 35.

Regarding claim 35, Cheung teaches fluorescent microspheres for detection of DNA (see Abstract). Thus it would have been obvious to one of ordinary skill in the art to use fluorescent microspheres for detection of DNA in the detection method of claim 35.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods of fluorescent detection of

Chen, Jeffreys, and Erlich et al. by using fluorescent microspheres as suggested by Cheung with a reasonable expectation of success. The motivation to do so is provided by Cheung who teach: "A single fluorescent microsphere is visible using standard fluorescent microscopy. Therefore the microspheres may be utilized not only to visualize cell surface anitgens but also DNA encoding for single genes, by means of a biotinylated DNA probe (see last two sentences of the Abstract). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Conclusion

21. No claim is free of the prior art.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Staples whose telephone number is (571) 272-9053. The examiner can normally be reached on Monday through Thursday, 9:00 a.m. to 7:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mark Staples/
Examiner, Art Unit 1637
August 1, 2009